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Synthesis method of hydroxyapatite: A review

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ABSTRACT

Hydroxyapatite (HAp) is most common calcium phosphate ceramic that is used in biomedical applications owing to its chemical composition, which is similar to human bone and teeth. Hydroxyapatite can be synthesised using chemical precursors, especially calcium and phosphorus, using various methods including, dry, wet, thermal, or a combination of these methods. Instead of using chemical synthesis, HAp can also be extracted from natural sources, such as animal bones and scales which are rich in HAp content. Different synthesising methods result in different morphologies, sizes, and phase crystallinities. The concern of achieving a nano-sized HAp has attracted a great deal of attention owing to the human bone HAp is in nano-size range, and the nano size HAp has excellent clinical performance compared to micron-sized HAp. Furthermore, production of nano-size HAp improves cell proliferation and cellular activity in bone growth, which makes it more suitable as biomaterials for bone implants. Thus, various parameters were studied to achieve a composition of HAp that is like the HAp in human bone and teeth. This review summaries various methods of synthesising the HAp, which includes dry, wet, thermal, and a combination of these methods.

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1. Introduction

Hydroxyapatite (HAp) is widely used in biomedical applications, especially in orthopaedic, odontology, as well as a coating material for metallic implants [1]. HAp is made up of 70% bone, while collagen comprises of 20% and water makes up 10% [2]. HAp has a chemical formula of $\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2$ instead of $\text{Ca}_5(\text{PO}_4)_3(\text{OH})$ because it contains two units in one single crystal [3]. According to Boskey [4], the hydroxide deficiency in bone apatite makes it called as 'hydroxyapatite' or 'apatite'. Besides of having a similar chemical composition with natural bone, HAp also possesses excellent biocompatibility, affinity to biopolymers, and has high osteogenic potentials thus it has been commonly chosen for various biomedical applications such as the bioactive coating on metallic osseous implants, middle ear implant, dental materials, and tissue engineering system [5]. Through many studies on HAp, it has been found that HAp may form into various structure and

size. Recently, nanosized HAp has been attracted a great deal of attention among the researchers. Also, nanosized HAp makes it easy for the researchers to understand the mechanism and design better biomedical devices for human such as for bone scaffold, bone filler, implant coating, and for drug delivery system. Many methods for the synthesis of HAp have been reported during the past decades. The complexity in producing the desired characteristic in HAp, such as the phase purity, crystallinity, stoichiometry, size, and morphology leads to further research to improve the method during the synthesising of HAp. In this review, the method of synthesising synthetic HAp is being discussed.

2. Synthesis of synthetic hydroxyapatite

Synthetic HAp can be synthesised using various techniques, which have been classified into dry, wet, and high-temperature methods [5]. Each of these methods results in different sizes, morphologies, and also yield different crystalline phases of the calcium phosphate besides pure crystalline HAp. Consequently, the characteristics of HAp significantly affect the bioactivity, mechanical, and

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biological properties. According to Cox [6], these characteristics determine the biomedical application of the HAp, thus, making it interesting to develop a synthesis method that can control the morphology, crystallinity, size and chemical composition of HAp. Thus, the study of each synthesis method is reviewed to conclude the differences and complexity of each method in the synthesis of synthetic HAp. Fig. 1 lists the different techniques used to synthesise synthetic HAp.

2.1. Dry method

Synthesising HAp using the dry method can be classified into two different methods, namely solid-state and mechanochemical methods. In the dry method, the precursor chemicals (calcium and phosphate), which are in a dry form, are mixed to synthesise the HAp. According to Sadat-Shojai et al. [5] most dry methods do not require precise and controlled conditions. This makes them suitable for the mass production of powders [5].

2.1.1. Solid state method

Solid-state reaction is defined as the decomposition reaction of a mixed solid reactant by heating it to produce new solids and gases [7]. The solid-state method is considered as a simple method in which the chemical precursors that contain calcium and phosphate are milled and calcined to obtain the HAp. According to Cox [6], the mechanism of this method is by the solid diffusion of the ion from chemical precursors (calcium and phosphate) followed by a high-temperature process to initiate the reaction [6]. Pramanik et al. [8] revealed that by using this solid-state technique, the calcium (CaO) and phosphate (P_2O_5) precursors are chemically combined to form the hexagonal structure of HAp [8]. The X-ray diffraction (XRD) pattern confirms that most of the sample's peak matches the monetite ($CaPO_3(OH)$) and calcium deficient HAp ($Ca_9(HPO_4)(PO_4)_5OH$). From that, it can be seen that the presence of many calcium phosphate phases using this solid-state method. Moreover, due to the small diffusion of ions during the solid-state reaction, the mechanochemical technique, which can improve the kinetics performance, was used as an alternative to this method [5]. On the other hand, Rao et al. [9] used solid-state reaction by applying tricalcium phosphate and calcium hydroxide ($Ca(OH)_2$) to synthesis HAp and β -Tricalcium phosphate (β -TCP). The chemicals were mixed in a different molar ratio of TCP to calcium hydroxide from 3:0 to 3:4, milled and heated at temperatures ranging from 600 °C to 1250 °C. The results showed that at a temperature of 1000 °C, different calcium phosphate phases are

formed with a different molar ratio of tricalcium phosphate and calcium hydroxide [9]. At a molar ratio of tricalcium phosphate and calcium hydroxide 3:2 and 3:3, the pure HAp was successfully synthesised. While at a molar ratio of 3:1 and 3:1.5, the biphasic mixture of HAp and β -TCP were formed. Calcium carbonate ($CaCO_3$) was used as the calcium precursor by Arkin et al. [10] and Koonawoot et al. [11], while di-calcium phosphate anhydrous ($CaHPO_4$) and ammonium dihydrogen phosphate ($NH_4H_2PO_4$) were used as the phosphate precursor by Arkin et al. and Koonawoot et al. respectively. Arkin et al. [10] reported that a high pure HAp was obtained after calcining at a temperature of 1300 °C for 7 h. Meanwhile, Koonawoot et al. [11] produced a mixture of HAp, TCP, and calcium oxide (CaO). The different calcination temperatures and time have been studied, and the results showed that the highest composition of HAp was achieved at a calcination temperature of 1250 °C for 2 h [11]. Table 1 lists some previous studies that employed the solid-state method for synthesising HAp.

2.1.2. Mechanochemical method

Mechanochemical is a technique that employs compression, shear, or friction via grinding and milling to induce a chemical transformation [12]. The mechanochemical techniques usually use ball-milling or planetary mills at certain speeds or frequencies. The high impact compression [13] and the increase in local temperature [14] during mechanochemical reaction contributes to the chemical reaction and enhances the diffusion process [15]. In order to overcome the limitation in controlling the air and moisture-sensitive substance, the mechanochemical method is usually conducted in a sealed vessel made from materials such as stainless steel, agate, zirconia, etc [12]. Sadat-Shojai et al. [5] stated that the mechanochemical technique produces a well-defined structure compared to the solid-state method that produces a heterogeneous particle with an irregular shape. Several variables in the mechanochemical method have been studied including the speed, milling time and mass ratio of the powder and ball. Fathi and Zahrani [16,17] had used the mechanochemical method in their study on the synthesis of fluoridated hydroxyapatite via mechanical alloying. Calcium hydroxide ($Ca(OH)_2$), phosphorous pentoxide (P_2O_5) and calcium fluoride (CaF_2) were mechanically mixed using the high energy planetary ball mill with zirconia vial and zirconia balls at ambient temperatures. Different milling times (15, 30, 60 min, and 2, 4, 6, 8, 10 and 15 h) were used with constant ball-to-powder weight ratio (35:1) at a rotational speed of 300 rpm. An XRD analysis of the samples showed that the calcium hydroxide phase had disappeared after milling for 15 min and the

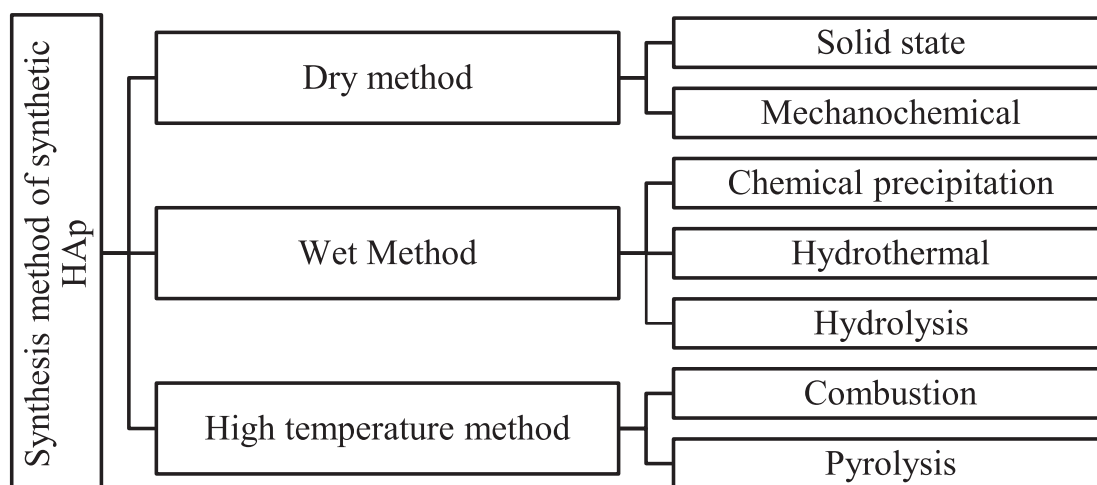


Fig. 1. Synthesis methods of synthetic HAp.

Table 1

Solid state method for synthesis of hydroxyapatite.

Method	Ca/P source	Result	Reference
Solid state	CaO, P ₂ O ₅	• Monetite and calcium deficient HAp	[8]
	β-TCP, Ca(OH) ₂	• HAp (Chemical ratio 3:2 and 3:3 at 1000 °C)	[9]
	CaCO ₃ , CaHPO ₄	• HAp (1300 °C)	[10]
	CaCO ₃ , NH ₄ H ₂ PO ₄	• 91.23% HAp, 5.27% TCP, 3.50% CaO (1250 °C for 2 h sintering)	[11]

Table 2

Mechanochemical method for synthesis of hydroxyapatite.

Method	Ca/P source	Result	Reference
Mechanochemical	Ca(OH) ₂ , CaF ₂ , P ₂ O ₅	• Fluorapatite (6 h) with size range from 35 to 65 nm	[17]
	Ca ₂ P ₂ O ₇ , CaCO ₃	• HAp	[18]
	CaHPO ₄ ·2H ₂ O, CaCO ₃ , CH ₄ N ₂ O	• Carbonated HAp (1 h)	[19]
	CaHPO ₄ , CaO	• Size: 50–150 nm in length and ~8 nm in width after milling for 24 h • HAp (>20–25 h) with size about 25 nm	[15]

CaF₂ phase was completely removed after milling for 30 min, indicating that the formation of apatite had begun [17]. The complete transformation of fluorapatite occurred after 6 h of milling. The fluorapatite's (Ca₁₀(PO₄)₆F₂) particle size ranged from 35 to 65 nm. In summary, this mechanochemical method is able to produce nano-sized fluorapatite with high purity. Rhee [18] used calcium pyrophosphate (Ca₂P₂O₇) and calcium carbonate to synthesis HAp using the mechanochemical technique. The reactant was milled at different milling times and then heat-treated at a temperature of 1100 °C for 1 h. The result showed that no phase changes occurred after milling, but rather after heat treatment. The results showed that the single-phase HAp was synthesised in the powder milled in water without the additional supply of water vapour during heat-treatment at a temperature of 1100 °C for 1 h [18]. The study explained that the mechanochemical reaction could supply enough amount of hydroxyl group to initiate the powder to form a single-phase HAp. Shu et al. [19] synthesised HAp by milling dicalcium phosphate dihydrate (CaHPO₄·2H₂O), calcium carbonate, and urea using a planetary ball mill containing 150 g of zirconia balls with a diameter of 10–15 mm. The XRD result showed that after 1 h of milling, the diffraction lines were detected in the HAp. However, an increase in milling time to 24 h did not change the XRD pattern, except that the peak became broader after 24 h of milling. The broadening of the peak indicates the reduction in crystallinity, which was due to the formation of carbonated HAp [19]. The transmission electron microscope (TEM) analysis showed that the size of HAp was in a range of 50–150 nm in length and ~8 nm in width after 24 h of milling. Yeong et al. [15] used a mechanochemical reaction to synthesise HAp using calcium hydrogen phosphate and calcium oxide precursors. The powder mixture had undergone mechanical activation in a high-energy shaker mill for 0 to 25 h. The mechanochemical reaction between calcium hydrogen phosphate and calcium oxide had produced highly pure HAp at >20 h of milling time [15]. The XRD result showed that increasing milling time results in a further increase in the crystallinity of HAp. Moreover, the nano-sized HAp was produced at a milling time of more than 20 h. The average particle size of 25 nm was produced after 25 h of milling.

It can be summarised that several different calcium and phosphate precursors were used for synthesising the HAp. A more prolonged mechanical activation will lead to the formation of HAp [15]. Besides, the result shows that prolonged milling time will also increase crystallinity and reduce HAp particle size [15]. Table 2 summarises the mechanochemical method used to synthesise the HAp.

2.2. Wet method

The wet method of synthesising HAp refers to the use of aqueous solution during the synthesis of HAp. Some of the wet methods usually used for the extraction of HAp include chemical precipitation, hydrolysis, and hydrothermal methods. Wet methods can control the morphology and mean size of the powder. Besides having these advantages, wet methods also have disadvantages, one of which is the HAp exhibiting low crystallinity owing to low processing temperatures [5].

2.2.1. Chemical precipitation

The chemical precipitation method is one of the broadest research techniques used for synthesising HAp. This method is widely used since a large amount of HAp can be synthesised at a reasonable cost [20]. The chemical precipitation method usually undergoes several processes. Firstly, calcium and phosphate containing reagents are mixed, such as calcium hydroxide or calcium nitrate as the Ca²⁺ source and orthophosphoric acid or diammonium hydrogen phosphate as the PO₄³⁻ source, according to the molar ratio of the HAp. This mixture is then adjusted to a specific pH, which usually is at an alkaline pH, and the temperature ranges from room temperature to the boiling point of water [21,22]. Next, the solution is stirred for ageing purposes, and lastly, the precipitates are washed, filtered, and dried before being crushed into powder form [5]. Yelten and Yilmaz [23] employed wet chemical precipitation by varying three process parameters, such as the reaction temperature (30 °C, 50 °C and 85 °C), acid addition rate (slow and rapid acid addition rates) and heat-treatment temperature (950 °C and 1250 °C) to produce HAp. The reaction of calcium hydroxide (Ca(OH)₂), and orthophosphoric acid (H₃PO₄) precursors were then proceeded by the maturation, decantation, and drying processes. The results showed that the precipitates at all parameters had successfully obtained a spherical-like morphology of the HAp [23]. The XRD result showed that a heat treatment at 1250 °C produces sharper peaks, which indicates more crystalline structure compared to heat treatment at 950 °C. Furthermore, Afshar et al. [24] also used calcium hydroxide and phosphoric acid to synthesise the HAp using the chemical precipitation method. The mixture was heated at a temperature of 40 °C and stirred vigorously for 1 h. After adjusting the pH, the solution was left overnight to allow precipitation to occur. The SEM micrographs showed that rod-like HAp with a size of approximately 200 nm in lateral and 50 nm in diameter were produced. On the other hand, Mobasherpour et al. [25] used calcium nitrate tetrahydrate

(Ca(NO₃)₂·4H₂O) and diammonium hydrogen phosphate ((NH₄)₂-HPO₄) as starting materials to synthesise the HAp using the chemical precipitation method. Ammonia solution was used for adjusting the pH. The reaction was initiated by vigorously stirring the calcium nitrate solution at a temperature of 25 °C. The diammonium hydrogen phosphate solution was slowly added to the calcium nitrate solution, and the pH was adjusted to 11. In order to obtain the powder, the solution was centrifuged and calcined for 1 h. The HAp was successfully synthesised using this method. The TEM micrographs indicated spherical-like HAp diameters of 8–20 nm. Recently, Peng et al. [26] had developed a new method that uses high-gravity precipitation technology to synthesise HAp. In this method, an aqueous solution of calcium nitrate tetrahydrate (Ca(NO₃)₂·4H₂O) and sodium phosphate (Na₃PO₄) are pumped in rotating packed beds at a high-gravity level of 1098 m/s² with a rotating speed of 1600 rpm. Then, the HAp precursor is collected and aged at room temperature overnight. The results show that the synthesised HAp has low crystallinity and short nano-rod structures with narrow-sized distributions at diameters of 1.9–14.2 nm and lengths of 4.0–36.9 nm. Moreover, the study suggested that the size of the HAp can be controlled by tuning the high-gravity level (rotating rate) during the precipitation process [26].

In summary, the chemical precipitation method needs several crucial processing parameters in order to synthesise the HAp. First, the chemical precursor used must be set according to the molar ratio of the HAp. An unbalanced molar ratio in the chemical precursor could result in the formation of another compound. Secondly, the pH of the mixture is an important factor that affects the production of HAp. Most studies had examined the optimal pH that can be used during the synthesising of HAp. According to Afshar et al. [24], the amount of Ca in the HAp precipitate decreases with decreasing pH. Thus, several processing parameters must be studied in order to maximise the production of HAp. Table 3 shows several previous studies that used chemical precipitation methods for synthesising HAp.

2.2.2. Hydrothermal

The hydrothermal method can be defined as the reaction method in aqueous media above the ambient pressure and temperature [27]. The hydrothermal method for synthesising HAp uses high temperature and pressure to stimulate a reaction in the solution containing calcium and phosphate precursors. The hydrothermal process occurs in an environment with a high temperature and pressure, such as inside an autoclave or a pressure vessel. The pressure and temperature increase the reactivity, and the effect of the condensation creates the chemical bonds and forms a nucleus that ensures the production of a relatively stoichiometric and highly crystalline HAp [28]. In addition, Huang et al. [27] stated that the synergistic effect of temperature and pressure is able to produce high crystalline materials without further post-treatment. Zhang et al. [29] used a hydrothermal method to synthesise HAp by mixing calcium chloride (CaCl₂) and phosphoric acid precursors. The mixture solution had undergone hydrothermal reaction at a temperature of 100 °C for 10 h. The XRD results show that the high purity HAp was noted. The morphology of the HAp is rod-shaped and

approximately 80 nm in length and 15 nm in width [29]. Moreover, Ortiz et al. [30] also employed the hydrothermal method to synthesise HAp using calcium hydroxide and ammonium phosphate (NH₄)₃PO₄ by autoclaving the solution at a temperature of 200 °C for 24 h. The results show that the HAp obtained was carbonated with a Ca/P ratio ranging from 1.86 to 2.08. The SEM micrographs reveal an irregular shaped HAp measuring 5–40 μm in size. Wang et al. [31] employed a low-temperature hydrothermal method with temperatures ranging between 60 and 150 °C for 12 to 24 h to synthesising the HAp using calcium chloride and dipotassium hydrogen phosphate (K₂HPO₄). The results show that pure crystalline HAp was obtained at a hydrothermal temperature of 120 °C for 12, 16, 20, and 24 h. The TEM micrographs reveal that the HAp obtained has a nano-rod shape with a diameter ranging from 15 to 20 nm and length from 60 to 75 nm [31]. Conversely, Nagata et al. [32] used the hydrothermal method on calcium nitrate tetrahydrate and diammonium hydrogen phosphate to synthesise HAp. The mixture was stirred at a temperature of 25, 60, 120, and 180 °C for 3 h. The results show that pure crystalline HAp was produced at pH 10 at each level of temperature (25, 60, 120, or 180 °C). The XRD patterns show that the increasing temperature results in sharper peaks, which indicates the increase in HAp crystallinity. The morphology of the HAp powder was granule-like in shape with aspect ratios of 1 and 30, 50, and 75 nm sizes [32]. As evident in the conventional hydrothermal method for synthesising HAp, the results show that the HAp has inconsistent shapes and sizes. In order to overcome this problem, several studies had used a surfactant, such as a cetyltrimethylammonium bromide (CTAB) [31,33] and a chelating agent, such as ethylene diamine tetraacetic acid (EDTA) [34], to control the HAp morphology [33]. However, some studies had used organic substances such as the sodium lignin sulfonate (SS) [35] and vitamin C [36] to overcome the problem of using synthetic surfactants that are costly, potentially toxic, and difficult to remove owing to its hydrophobic property [35]. The use of this modifier in the hydrothermal treatment had been proven to help control the shape of the HAp particle. Hoai et al. [33] added the CTAB to diammonium hydrogen phosphate and calcium during the hydrothermal reaction. The results show that the nano-rod shaped HAp was synthesised and the mean length of the nano-rod increased slightly from 133 nm to 158 nm in length as the amount of CTAB increased. The results helped conclude that the amount of surfactant used affects the length of the particle, in which the smallest particle measuring 133 nm in length and 40 nm in diameter was produced using 0.64 g of CTAB.

In summary, the hydrothermal method can produce HAp with higher crystallinity compared to the chemical precipitation method. Moreover, this method can synthesise the controllable size and morphology of the HAp powder by adding modifiers such as the CTAB and EDTA. Table 4 shows several studies that used the hydrothermal method for the synthesis of HAp.

2.2.3. Hydrolysis

Hydrolysis is one of the wet methods least used for the synthesising HAp. Basically, hydrolysis is defined as a water ionisation process that causes the diffusion of hydrogen and hydroxide ions

Table 3
Chemical precipitation method for synthesis of HAp.

Method	Ca/P source	Result	Reference
Chemical precipitation	Ca(OH) ₂ , H ₃ PO ₄	• HAp with spherical like shape and particle size in range of 0.2–1.6 μm	[23]
	Ca(OH) ₂ , H ₃ PO ₄	• Rod-like, with approximately 200 nm in lateral and 50 nm diameter.	[24]
	Ca(NO ₃) ₂ ·4H ₂ O, (NH ₄) ₂ HPO ₄	• Almost spherical, with particle size 8–20 nm diameter	[25]
	Ca(NO ₃) ₂ ·4H ₂ O, Na ₃ PO ₄	• Short nano-rod, with diameters 1.9–14.2 nm and lengths 4.0–36.9 nm	[26]

Table 4

Hydrothermal method for synthesis of hydroxyapatite.

Method	Ca/P source	Temperature (°C)	Result	References
Hydrothermal	CaCl ₂ , H ₃ PO ₄	100	• HAp with rod-like shape (80 nm length and 15 nm width)	[29]
	Ca(OH) ₂ , (NH ₄) ₃ PO ₄	200	• Irregular agglomerate shape (5–40 μm) of carbonated HAp	[30]
	CaCl ₂ , K ₂ HPO ₄	60–150	• Ca/P ratio: 1.86–2.08	
	Ca(NO ₃) ₂ ·4H ₂ O, (NH ₄) ₂ HPO ₄	25–180	• HAp (120 °C) with rod-like shape (15–20 nm diameter and 60–75 nm length)	[31]
			• HAp (pH 10) with granule-like shape (30, 50, and 75 nm)	[32]

[37]. Thus, the hydrolysis of calcium phosphate could result in the formation of a non-stoichiometric HAp [37]. Nakahira et al. [38] employed water and organic solvents (ethanol, 1-butanol, 1-hexanol, and 1-octanol) for the hydrolysis of the α -TCP to HAp. The α -TCP was mixed with five different solvents stirred for 2–120 h at 70 °C. The result shows that a different solvent system needs a different amount of time to completely transform the α -TCP to HAp. The use of water and 1-hexanol as solvents takes 24 h to completely transform the α -TCP to HAp, while 1-octanol takes longer than 24 h. However, the use of 1-butanol requires more than 72 h to transform α -TCP to HAp, and the use of ethanol delays the transformation of α -TCP to HAp. The TEM micrographs show that HAp exhibits whisker-like and platelet-like structures. In another study, Sinitsyna et al. [37] also used α -tricalcium phosphate to synthesis the HAp, in which the α -TCP suspension and distilled water were maintained at temperatures of 20, 40, 60, and 100 °C. The results show that the HAp was fully transformed after 48 h of hydrolysis at a temperature of 40 °C. However, it only took 3 h for the HAp to completely transform when the hydrolysis was carried out at 100 °C.

Mechay et al. [39] used the polyol medium (propane diol and ethylene glycol) in the hydrolysis process of calcium nitrate and diammonium phosphate. During the hydrolysis process, the calcium nitrate was added drop by drop into the solution containing diammonium phosphate. The hydrolysis was carried out at a temperature of 136 °C for 3 h, and the pH was adjusted to 10 before leaving it for the maturation process. It was found that for both solvents, a complete transformation of HAp occurred. The TEM micrographs show that HAp exhibited needle and plate-like structures with lengths varying from 140 to 180 nm and widths from 60 to 80 nm with almost constant thickness (15–20 nm) [39]. Whereas, Wang et al. [40] used different concentrations of the solvents to hydrolyse the calcium hydrogen phosphate dihydrate (DCPD) into HAp. Different concentrations of alcohol from 0 to 90 % were used during the experiment. A mixture of DCPD with the solvent, sodium hydroxide and cetyltrimethylammonium bromide (CTAB) underwent the hydrolysis process at a temperature of 75 °C for 1 h. It was found that all samples were successfully transformed into HAp. Meanwhile, the alcohol concentration had affected the crystallite size of the HAp. The crystallite size decreased as the concentration of alcohol increased from 0 to 70 %, while the crystallite size increased as the alcohol concentration increased from 70 to 90 %.

In summary, the hydrolysis method was able to transform the calcium and phosphate precursors to a high purity HAp. Yet, most of the hydrolysis methods require long processing hours to complete the transformation of HAp. Table 5 shows the list of several studies that employed the hydrolysis process to synthesis HAp.

2.3. High-temperature method

HAp can also be synthesised using a high-temperature method where high temperature is used to decompose the materials. The high-temperature method consists of different methods, namely combustion and pyrolysis. Throughout all the synthesis methods of HAp, the combustion and pyrolysis methods were rarely used

for synthesising HAp. This is because it has poor control over the processing parameter and the production of secondary aggregates [5].

2.3.1. Combustion

The combustion technique uses rapid exothermic and self-sustaining redox reactions between the oxidant and organic fuel in an aqueous phase [5]. The reaction starts by heating the mixture at a low temperature before a sudden increase in the temperature. The final step in this process is the rapid cooling, which induces the nucleation and also prevents any further particle growth [5]. Sasikumar and Vijayaraghavan [41] used calcium nitrate and diammonium hydrogen phosphate as calcium and phosphate sources and citric acid and succinic acids as fuels. The precipitates underwent combustion at a temperature of between 185 and 425 °C, followed by the calcination process at 900 °C for 2 h to produce hydroxyapatite. The results showed that the carbonated HAp was formed through the combustion of the citric acid or the succinic acid. Also, the β -tricalcium phosphate was formed when it underwent combustion using the mixture of citric and the succinic acids [41]. Meanwhile, Canillas et al. [42] employed calcium nitrate tetrahydrate and diammonium phosphate as the calcium and phosphate source and urea as the fuel for the combustion process. The XRD results showed that the HAp was produced as a major phase and β -TCP as a minor phase. Kavita et al. [43] used calcium acetate and diammonium phosphate for synthesising the HAp through combustion method. The mixture was adjusted to pH 7.4 using the tris hydroxyl methyl aminomethane. Then, the urea was added as fuel for the combustion process, and the ignition temperature was kept at 500 °C for 3, 5, 10, 20, and 30 min. The results showed that the pure crystalline HAp phase was synthesised at 30 min of the combustion process. Furthermore, Narayanan et al. [44] used the same combustion temperature but different chemical precursor and reaction time. The calcium nitrate, ammonium dihydrogen phosphate, and calcium hydroxide were combusted by addition of urea at a temperature of 500 °C for 15 min. The results revealed that the HAp with CaO phases were observed in the XRD pattern. Table 6 lists several previous studies that used combustion methods for synthesis of HAp. Therefore, this combustion method can produce a highly crystalline HAp, but the result showed that there other phase impurity present besides HAp.

2.3.2. Pyrolysis

The pyrolysis technique involves the spraying of a precursor substance into a hot zone of the electric furnace [28]. Sadat-Shojai et al. [5] stated that pyrolysis products had been used as post-treatments to achieve a high crystalline product. In comparison with the combustion method, it is not necessary to mix fuel with reactants in the pyrolysis synthesis, and the process can be easily scaled up for continuous production of HAp particles. It should be mentioned that the pyrolysis method can also be classified under a broad category generally known as aerosol methods (or gas-phase methods), in which gas-to-particle or liquid-to-particle conversions occur in an aerosol decomposition process.

Table 5

Hydrolysis methods for synthesis of hydroxyapatite.

Method	Ca/P source	Solvent	Result	Reference
Hydrolysis	α -TCP	<ul style="list-style-type: none"> Water Water + ethanol Water + 1-butanol Water + 1-hexanol Water + 1-octanol Water 	<ul style="list-style-type: none"> HAp (24 h) HAp + α-TCP HAp (<72 h) HAp (24 h) HAp (<24 h) HAp (48 h at 40 °C) HAp (3 h at 100 °C) 	[38]
	α -TCP			[37]
	$\text{Ca}(\text{NO}_3)_2 \cdot (\text{NH}_4)_2\text{HPO}_4$	<ul style="list-style-type: none"> Propane diol (PD) Ethylene glycol (EG) 	<ul style="list-style-type: none"> HAp HAp 	[39]
	DCPD	<ul style="list-style-type: none"> NaOH + alcohol + (CTAB) 	<ul style="list-style-type: none"> HAp 	[40]

Table 6

Combustion method for synthesis of hydroxyapatite.

Method	Ca/P source	Fuels	Combustion temperature (°C)	Result	Reference
Combustion	$\text{Ca}(\text{NO}_3)_2 \cdot (\text{NH}_4)_2\text{HPO}_4$	Citric acid, succinic acids	185–425	<ul style="list-style-type: none"> Ca/P ratio: 1.67 TCP (major) in mixture of fuel Single fuel results in carbonated HAp. HAp (major) and β-TCP (minor) 	[41]
	$\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, $(\text{NH}_4)_2\text{HPO}_4$	Urea	500		[42]
	$\text{Ca}(\text{C}_2\text{H}_3\text{O}_2)_2 \cdot (\text{NH}_4)_2\text{HPO}_4$	Urea	500	<ul style="list-style-type: none"> HAp (ignition temperature of 500 °C at a pH of 7.4 with 30 min) Small nanorods with smooth edges of diameter 5 ± 2 nm and length ≥ 17 nm 	[43]
	$\text{Ca}(\text{NO}_3)_2$, $\text{NH}_4\text{H}_2\text{PO}_4$, $\text{Ca}(\text{OH})_2$	Urea	500	<ul style="list-style-type: none"> HAp and CaO phases Rectangular 	[44]

Table 7

Pyrolysis method for synthesis of hydroxyapatite.

Method	Ca/P source	Result	Reference
Pyrolysis	$\text{Ca}_3(\text{PO}_4)_2$, $\text{Ca}(\text{NO}_3)_2 \cdot 4\text{H}_2\text{O}$, $(\text{NH}_4)_2\text{HPO}_4$	<ul style="list-style-type: none"> Hollow sphere with size 1–4 μm 	[46]
	$\text{Ca}(\text{C}_2\text{H}_3\text{O}_2)_2$, $(\text{NH}_4)_2\text{HPO}_4$ <ul style="list-style-type: none"> $\text{Ca}(\text{NO}_3)_2$, $(\text{NH}_4)_2\text{HPO}_4$, HNO_3 $\text{Ca}(\text{OH})_2$, H_3PO_4 $\text{Ca}(\text{C}_2\text{H}_3\text{O}_2)_2$, $(\text{CH}_3)_3\text{PO}_4$ 	<ul style="list-style-type: none"> HAp HAp HAp, β-$\text{Ca}_3(\text{PO}_4)_2$ Irregular and flat shape smaller than 10 μm (913 K) Irregular and flat shape smaller than 40 μm (1013 K) HAp β-$\text{Ca}_3(\text{PO}_4)_2$ HAp, CaCO_3 	[47] [48]

The pyrolysis method or sometimes known as 'spray pyrolysis', involves spraying precursor solutions into a flame or a hot zone of an electric furnace using an ultrasonic generator. This process is then followed by the reaction of the generated vapours and gases at high temperatures to produce the final powder, typically in an aggregated and agglomerated form [45]. The high temperature leads to the complete evaporation of precursor droplets followed by nucleation and growth of nanoparticles in the gas phase. Cho et al. [46] conducted spray pyrolysis by mixing calcium phosphate, calcium nitrate tetrahydrate, and diammonium hydrogen phosphate at 1100 °C with a carrier gas flow rate of 40 L/min. The XRD result shows that the HAp phases were obtained using this method. The FESEM micrograph shows that the HAp powder has a micron-sized spherical shape. Widiyastuti et al. [47] used a mixture of calcium acetate and diammonium hydrogen phosphate to synthesise HAp using the spray pyrolysis method. The aqueous mixture was atomised to generate droplets using the ultrasonic nebuliser. The droplet from the atomised precursor solution with a flow rate of 1 L/min was heated at 500, 700, 900, and 1000 °C. The SEM analysis shows that the particle size synthesised by the spray pyrolysis method produced by hollow-shape morphology. This is due to the solvent droplet's rate of evaporation being faster than the rate of solute diffusion [47]. The XRD pattern shows that

no dominant HAp phase was observed at the lowest temperature, while at 1000 °C, the HAp pattern appeared. Nakazato et al. [48] had used several calcium and phosphate precursors for synthesising HAp using the drip pyrolysis technique. The drip pyrolysis technique using chemical precursors was carried out in a fluidised bed, where the slurry droplet had undergone a pyrolysis reaction to continuously produce HAp. The temperature of the fluidised bed was set in the range of 913–1113 K for 0.7–7 h. The SEM micrograph of the calcium nitrate and ammonium phosphate mixture shows that at a temperature of 913 K, the particles had an irregular and flat shape with particle sizes smaller than 10 μm . However, at a temperature of 1013 K, most of the particle size was larger than 40 μm . The XRD result shows that the use of different calcium phosphate precursors produces different calcium phosphate phases besides HAp. Table 7 summarises several studies that used pyrolysis for synthesising HAp.

3. Conclusion

Therefore, it can be concluded that various methods can be used for synthesising synthetic HAp. Each method requires several processing parameters such as pH, temperature, the molar ratio of

chemicals, etc. in order to produce the pure HAp phase. It can also be concluded that a balanced molar ratio of calcium and phosphate precursors must be used in order to produce the stoichiometric HAp. pH, as another parameter, also plays an important role in some of the methods used for synthesising HAp. Moreover, the use of organic modifiers, such as CTAB and EDTA, were recently used to control the morphology of the HAp particle. Thus, a HAp particle with a uniform shape and size can be achieved. In addition, the method for synthesising synthetic HAp provides various techniques that help produce various characteristic of HAp, such as different sizes, morphology, and also the HAp phase. Despite the variety of methods used for preparing HAp nanoparticles, only a few of them are satisfactory in terms of economics or performance. This is mainly due to the diverse materials needed for the synthesis, complicated and expensive processes, severe aggregation and agglomeration, wide particle size distribution, and various phase impurities that usually occur in the crystal structure. Thus, other alternatives, such as extracting the HAp from a natural source, could alleviate the problem of producing synthetic HAp. The animal bone and scale, which are composed of HAp, can be a good source for producing HAp, and it has all the good trace elements that can enhance the biological properties of HAp.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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